A Prospective Non Randomized Clinical Study to Evaluate the Role of Direct Percutaneous Ethanol Instillation in the Treatment of Venous Malformations (VMs) in the Face and Neck

A dissertation submitted to the Tamil Nadu Dr. M.G.R. Medical University in the partial fulfillment of the requirement for the award of M.Ch. Branch III (Plastic Surgery) degree August 2007-2010.

CERTIFICATE

I hereby declare that this dissertation entitled "**A Prospective Non Randomized Clinical Study to Evaluate the Role of Direct Percutaneous Ethanol Instillation in the Treatment of Venous Malformations in the Face and Neck"** is a bonafide research work carried out by Dr. Shashank Lamba in partial fulfillment of the requirement for the degree of the requirement for the degree of M.Ch. in Plastic Surgery.

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This is to certify that this dissertation entitled "**A Prospective Non Randomized Clinical Study to Evaluate the Role of Direct Percutaneous Ethanol Instillation in the Treatment of Venous Malformations in the Face and Neck"** is a bonafide and genuine research work carried out by Dr.Shashank Lamba under the guidance of **Dr. Ashish Kumar Gupta** M.S, Mch Professor and Unit head, Department of Plastic Surgery, Christian Medical College, Vellore.

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Introduction

Venous malformations are composed of thin-walled channels, deficient in smooth muscle, that are lined by quiescent endothelium. They usually occur in a pure form; however, they can be combined, such as capillary-venous malformation or lymphatic-venous malformation. These malformations are usually congenital (i.e., obvious at birth), but they also often appear in childhood or adulthood. They grow proportionately with the patient and do not regress.[9]

Symptoms are related to size and location. Many venous malformations are superficial cutaneous blemishes. Deep cutaneous or intramuscular lesions usually cause discomfort, often in the early morning on awakening or with exertion. Intraoral venous malformations can bleed, distort dentition, cause speech problems, or obstruct the upper airway and pharynx. Thrombosis, swelling, and pain are common in all venous malformations. The most accurate radiologic techniques for delineating venous malformations are magnetic resonance imaging (MRI) and direct injection venography. These anomalies exhibit high signal intensity on spin-echo T2-weighted MRI sequences. They opacify poorly or not at all by arteriography.[19]

The various modalities of treatment are either surgical or non surgical. Complete excision seldom achieved because of the complicated facial anatomy and usually may lead to nerve damage, massive bleeding and cosmetic deformity. Among the non surgical ones sclerotherapy is the most preferred. It acts by obliteration of the channel lumens by damaging endothelium with subsequent inflammation & fibrosis. Thus, it has advantages of few complications and no external scarring

The two most common agents used are Ethanol and Sodium tetradecyl sulphate. Sodium tetradecyl sulphate has drawback that a limited dose can be given in one sitting thus requiring multiple sessions. It is also less potent as compared to ethanol with greater tendency for recanalization.

Ethanol on the other hand can be given upto 1ml/kg body weight .It is the most reliable sclerotherapeutic substance with lowest rate of malformation recurrence.Thus, keeping in view above facts we planned to evaluate the role of direct percutaneous ethanol instillation in venous malformations of the face and neck**.**

Aims and Objectives

1. To evaluate the efficacy of Direct Percutaneous Ethanol Instillation in Venous Malformation of the Face and Neck.

2. To study the side effects of ethanol sclerotherapy in venous malformations of face and neck.

3. To study factors that might predict the result of sclerotherapy.

Materials & Methods

This is a one and half years prospective study from July 20, 2008 to December 31, 2009 of fifteen patients with the diagnosis of venous malformation in the face and neck treated with direct percutaneous ethanol instillation in the Department of Plastic Surgery, Christian Medical College & Hospital, Vellore. Informed consent was obtained from all the patients. This study was approved by the Institutional Review Board of the Christian Medical College & Hospital, Vellore.

Procedure

The diagnosis was confirmed by a combination of history, physical findings and Magnetic Resonance Imaging. Percutaneous Ethanol (99.5% ethyl alcohol) Sclerotherapy was given in the DSA Room under all aseptic precautions by experienced Radiologists. After the induction of general anesthesia, intravenous fluid was administered, a urinary catheter was placed, and the facial site prepared and draped in a sterile manner. Rubber Bands were used to compress the patient's forehead and chin to occlude the facial venous return. Under ultrasound guidance, venous spaces were cannulated using one or more no. 23G scalp vein needles, Blank Road Map was taken and contrast Medium was under DSA (Siemens Multistar) till the deep vein opacification was seen. The volume of contrast injected by syringe was used to determine the volume of venous cavities. Any contrast injection draining immediately to deep vein was avoided for sclerotherapy. The course of the deep veins also evaluated, especially to exclude any intracranial course of the deep veins.

Fig (1) Rubber bands to occlude the facial venous return

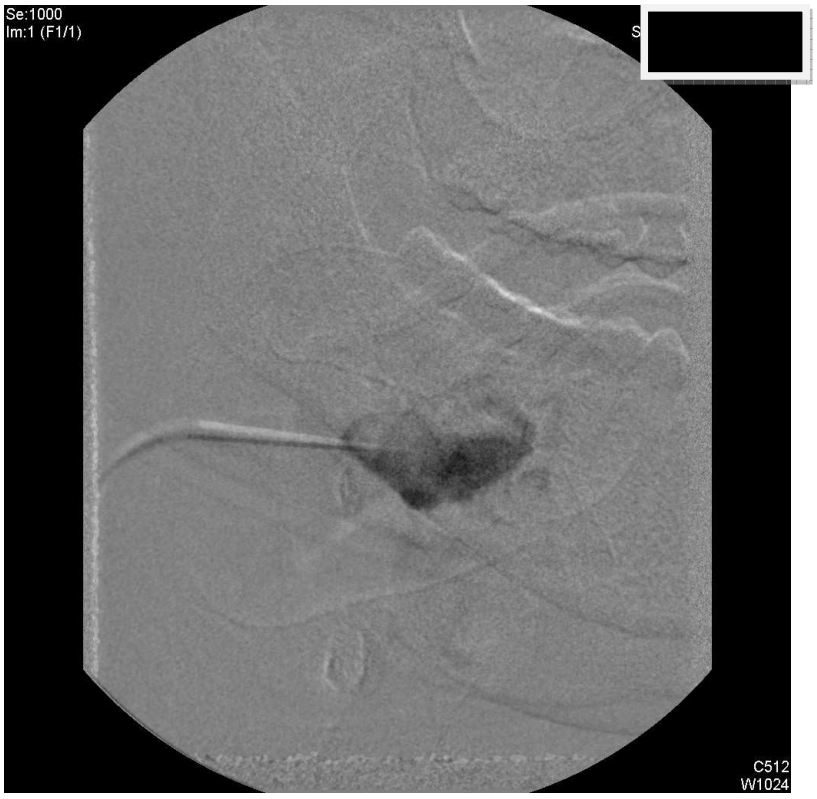


Fig (2) DSA showing contrast in the background of Blank Road Map

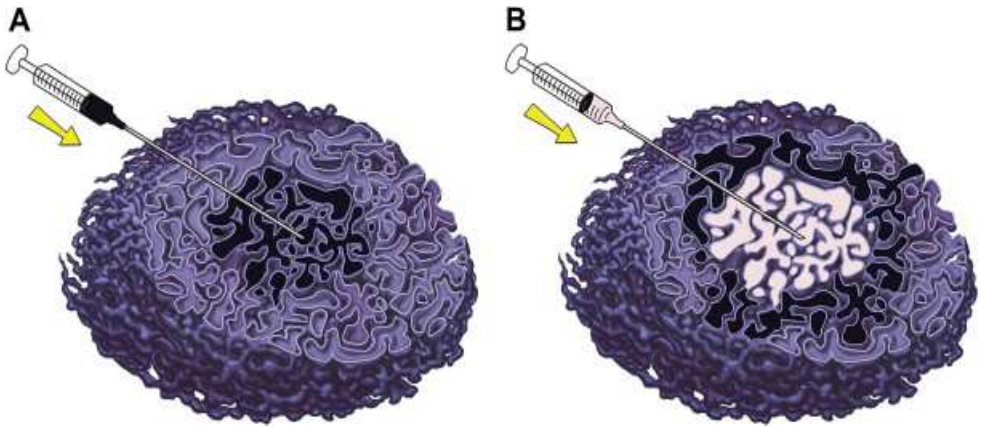


Fig (3) Contrast being injected

Fig (4) Ethanol injection being administered in the cavity.

After assessing the volume of cavity; injection of 99.5% ethanol one third the cavity volume (not exceeding the maximum recommended dose of 1ml/kg body weight) was injected into the tumor cavities under DSA and catheter was withdrawn. Manual compression was maintained for 5 minutes to fix the solution in the clot and the vein walls. All patients received intravenous hydration for 4 to 24 hours after sclerotherapy, generally at twice the maintenance rates. Urinary output was monitored for volume and color. All the patients were observed overnight in the hospital. All the patients were given a corticosteroid, 0.1 mg/kg dexamethasone, immediately before the procedure and every 8 hours while in the hospital. After discharge from the hospital, prednisolone was given at 2 mg/kg/day in three divided doses, which was tapered over 5 days. Repeat course of injection 99.5% ethanol was administered after an interval of 12 weeks from the previous injection if abnormal venous channels persisted. Treatment success was determined by reduction in lesion size on MRI. All the patients were followed up for a minimum of 3 months after the last session of sclerotherapy and were graded by the following grading criteria:

Grading

Good	Complete Disappearance of symptoms including clinical obliteration
Fair	Decrease in size and symptoms
Poor	Little or no improvement

Inclusion Criteria: All patients between 2 years and 65 years of age

Exclusion Criteria: All patients below 2 years and above 65 years of age.

Statistical Analysis

The following statistical method has been applied:

1. Paired t test
2. Spearman's rank correlation coefficient
3. Scatter plot

Review of Literature

Venous malformations (VMs) are a commonly encountered entity in clinical practice, with an estimated incidence of 1 to 2 in 10,000[1] births and a prevalence of 1%[2] and [3].

For several centuries, a myriad of cutaneous or visceral masses, pigmentations, or spaces that resulted in a predominantly disturbed vascular morphologic pattern were named and categorized according to appearance, location, fluid content, and often inconsistent or unpredictable clinical behaviour.[4]

Until only recently, this purely descriptive nomenclature resulted in a severely bloated lexicon that was redundant, difficult to understand or conceptualize, and predisposed to frequent misdiagnosis and incorrect management.[5] Further understanding of etiology, disease process relationships, and the development and testing of novel therapies was also impeded because these earlier categorization schemes were not founded on the currently accepted belief that a much smaller group of vascular defects or entities are responsible for the protean clinical appearances and manifestations of most vascular anomalies.

Over time, experienced multidisciplinary vascular anomaly teams have evolved that allow the establishment of clear lines of communication and the use of the most current clinical, pathologic, and image-based standards available.[6-8]

Historical Background

Because most vascular anomalies involve the skin to variable degree they tend to be visible and have consequently received colorful appellations since ancient times. As recently as the nineteenth century, causative factors implicating

the mother resulted in names such as naevus maternus or “mother's mark.”[9] Other systems used food descriptors, such as strawberry, port-wine, or cherry, terms that unfortunately still persist in common medical parlance today.[5]and[10] Virchow and Wegner developed histologic-based classification schemes for vascular anomalies in the later nineteenth century. Vascular lesions were considered to be vascular tumors and were further subdivided into angioma simplex (later known as the “capillary” or “strawberry” hemangioma); angioma cavernosum (later used to describe both the infantile hemangioma or the VM); and the angioma racemosum (used to describe a cirsoid aneurysm or arteriovenous hemangioma).[5],[9],[10], [11]and[12] This classification hypothesized an underlying cause of abnormal vascular cellular proliferation or dilatation at work, but did little to address the biologic behavior of these lesions.[10] As early as 1932, De Takats[13] proposed that these angiomas represented persistent rests of embryonic angioblastic tissue that failed to resorb fully or differentiate because of aberrations in vasculogenesis occurring in specific stages of embryonic development. The concept of these lesions being tumors persisted in the literature,[14] however, fostering the ubiquitous use of the term “hemangioma” that was often accompanied by host of prefixes. This practice continued throughout the remainder of the twentieth century, perpetuating the disconnect between misleading nomenclature and the true biologic nature of the lesion its name was meant to describe.

By 1971, there was general agreement by attendees of the International Symposia on Angiological Nosology in Florence that a new vascular anomaly classification scheme “was absolutely necessary for didactic and practical purposes” that was to be “in so far as possible, schematic and simplified.”[15] As a

result, based on the concepts proposed by Malan[16] and described by Degni and coworkers,[17]and[18] congenital vascular defects were simply categorized as predominantly arterial, venous, arteriovenous, lymphatic, or mixed.

In 1982, in a landmark publication, Mulliken and Glowacki[9] proposed what would become the foundation of modern vascular anomaly classification. Based on the lesion's biologic and pathologic differences, all vascular anomalies were assigned to one of two broad categories: hemangiomas and vascular malformations (Table 1).

Hemangiomas were described as those exhibiting rapid neonatal growth and hypercellularity during a proliferating phase, followed by an involutive phase characterized by diminished cellularity and fibrosis. This former category was later expanded to include vascular tumors. The suffix “-oma” was only to be reserved for those lesions exhibiting increased cellular turnover, the classic example within this category being the infantile hemangioma.

The term “vascular malformation” was applied to those lesions present at birth growing commensurately or pari passu with the child. The vascular malformations were composed of normal “mature” flat endothelial-lined vascular spaces with normal rates of cell turnover and were further subdivided into capillary malformation; VM; arterial (arteriovenous malformation [AVM]); lymphatic malformation (LM); and fistulae initially. In 1983, Burrows and coworker[13] incorporated angiographic differentiation and flow characteristics into the classification.

Table -1

Classification of vascular lesions in infants and children

Hemangiomas	**Malformations**
Proliferating phase	Capillary
Involuting phase	Venous Arterial Lymphatic Fistulae

In 1988, at the 7th Meeting of the ISSVA in Hamburg, the work of Malan, Degni, and Belov formed the “Hamburg Classification” of vascular defects (Table 2).

In 1993, Jackson and coworkers[20] later identified the need for further augmentation of Mulliken's classification to “answer the (therapeutic) questions of ‘what to do’ and ‘when to do it’.” He elegantly simplified flow patterns within vascular malformations as either low flow (VMs) or high flow (AVMs), keeping separate categories for LMs and hemangiomas, with the purpose of creating a “system directly related to investigation and treatment” (Box 1). LMs have since been subdivided into macrocystic, microcystic, and mixed varieties based on lesion cavity size. For simplicity, many now consider LMs to reside in Jackson's low-flow category

Table - 2

Anatomopathologic classification of vascular defects (Hamburg classification)

Type	Forms	
	Truncular	**Extratruncular**
Predominantly arterial defects	Aplasia or obstructive	Infiltrating
	Dilatation	Limited
Predominantly venous defects	Aplasia or obstructive	Infiltrating
	Dilatation	Limited
Predominantly lymphatic defects	Aplasia or obstructive	Infiltrating
	Dilatation	Limited
Predominantly AV shunting defects	Deep	Infiltrating
	Superficial	Limited
Combined/mixed vascular defects	Arterial and venous	Infiltrating hemolymphatic
	Hemolymphatic	Limited hemolymphatic

Box- 1

Classification of vascular anomalies by vascular dynamics

I. Hemangioma
II. Vascular malformations
a. Low-flow (VM)
b. High-flow (AVM)
III. LM

In 1992 at the ISSVA meeting in Colorado, a final nosologic consensus clarified the umbrella term of “vascular anomaly” to describe all vascular tumors and malformations and the use of the suffix “-oma” to refer only to lesions demonstrating cellular hyperplasia.[21] The final modern classification of vascular anomalies after Mulliken based on histology, clinical behavior, and flow characteristics was adopted at the ISSVA in Rome 1996,[21] with the most recent and complete version appearing in 2007 (Table 3).[22]

Table - 3

International society for the study of vascular anomalies classification of vascular anomalies

Tumors	**Vascular Malformations**	
	Simple	**Combined**
Infantile hemangioma	Capillary (C)	Arteriovenous fistula
Congenital hemangioma	Lymphatic (L)	Arteriovenous malformation (AVM)
Tufted angioma	Venous (V)	CVM
Kaposiform hemangioendothelioma		CLVM
Hemangiopericytoma		LVM
Pyogenic granuloma		CAVM
Spindle-cell hemangioendothelioma		CLAVM

Gross Inspection

VMs are composed of abnormal collections of veins that have a variable luminal size and wall thickness and geographically can appear superficial, deep, diffuse, localized, and not uncommonly multiple.[23] The lesions are often less well circumscribed than vascular tumors, such as infantile hemangiomas[23], and can be interspersed with adipose tissue or within variably atrophic or degenerative muscle.[8] and [24]

Conventional Microscopy

As with all vascular malformations, conventional hematoxylin-eosin staining techniques for VMs reveal irregular variably dilated or thickened dysplastic-appearing vascular channels lined with flat mature endothelial cells in contrast to hypercellularity seen in vascular tumors.[9],[10],[23]and[24] These vascular spaces are usually filled with an abundance of erythrocytes. Capillaries and venules may reside within the VM substance. In addition to the absence of internal elastic lamina, there is a relative paucity or intermittent absence of smooth muscle within the VM channel wall[8]and[23] with occasional locules of disorganized smooth muscle identified emanating from the vascular wall into the surrounding stroma[23] Localized intravascular coagulopathy is frequently present within VMs[25] and as a result, luminal thrombi can develop and become calcified and form phleboliths.

Immunohistochemical Staining

Although the vascular channels in VMs are surrounded by a normal reticulin network,[9] anti-smooth muscle α-actin stains reveal an absent or patchy mural smooth muscle distribution in clumps, which is thought to be the major causative factor in the histologically observed vascular ectasia that results in the mass-like appearance of VMs.[26], [27], [28] and 29]

In cases of mixed or ambiguous histology, the addition of immunohistochemical staining to a detailed clinical and imaging work-up may be required to arrive at the correct diagnosis. All vascular malformations are negative for glucose transporter-1 that is expressed exclusively by infantile hemangiomas.[30] D2-40, a monoclonal antibody to oncofetal antigen M2A, is highly avid for normal lymphatic endothelium and interestingly also within kaposiform hemangioendotheliomas.[31],[32],[33]and[34] This allows discrimination between VMs and frequently similar appearing LMs (particularly microcystic varieties) with the former staining negative for this antibody and the latter staining positive.[33]

Developmental etiology of venous malformations

Because many vascular malformations are not clinically obvious in early life, it is not generally appreciated that all vascular malformations are present at birth.[23] For that reason, it has long been held that a localized defect or defects within vascular morphogenesis is responsible for all vascular malformations whether caused by hereditable or sporadic mutation, altered gene expression, or environmental factors. To comprehend the hypothesized mechanisms leading to

the development of a VM, one must first possess an understanding of normal vascular morphogenesis.

Embryology: Vascular Morphogenesis

The cardiovascular system is the first functional system to form in the embryo[35] and begins development at approximately 13 to 15 days gestation with the urgent embryonic need for increased nourishment and oxygenation. Vascular morphogenesis is divided into two phases. The first phase, termed "vasculogenesis," begins in the extraembryonic mesoderm of the yolk sac.[36] Mesodermal hemangioblasts congregate into clusters of blood islands that cavitate centrally. Outer layers differentiate into endothelial progenitors called angioblasts,[37] whereas the inner layers form primitive plasma and blood cells.[36] These "shells" organize to form a lattice of short tubes or canaliculi that constitute the primary capillary plexus. The second phase, angiogenesis, occurs as a result of four distinct processes.[38],[39]and[40] Sprouting results in additional capillaries "budding" from existing capillaries. Nonsprouting occurs as a result of extracellular matrix transcapillary pillars or posts cleaving or fusing existing vessels. These first two processes occur simultaneously on the primary capillary plexus to create a juvenile vascular network. Further deletions are made in the juvenile network through the third process of pruning. The fourth and final process, termed "maturation," occurs as a result of an interaction between the primitive endothelium and the surrounding mesenchyme to form fully differentiated smooth muscle cells and pericytes-adventitia surrounding mature endothelium. This gives rise to a fully differentiated multilayered vascular structure within a mature circulatory system.

Molecular Genetics: Endothelial-Pericyte Interactions

Given the histologic abnormalities of the smooth muscle–pericyte component within vascular channel walls of VMs, it is not surprising that a hypothesized defect in this interaction has garnered a great deal of attention by molecular biologists as a potential cause of many VMs.[38] In a recent study of 1685 patients, 98.8% of VMs occurred sporadically in a noninherited fashion.[41] The few inherited varieties often appear as multifocal lesions clinically.[42],[38]and[43] Some entities are thought to be the result of mosaicism.[44] The molecular biologic study of these inherited lesions allows a more complete understanding of the genes coding for endothelial cell–mesenchymal pericyte interaction and those genes and proteins that are responsible for the observed malformation phenotypes.[1], [42], [26], [30], [28], [35], [45], [46], [47] and [48]

The study of a rare autosomal-dominant inherited condition named "familial cutaneomucosal VM," characterized by the appearance of multiple cutaneous and mucosal VMs within two separate families, reveals a genetic linkage to a locus on the short arm of chromosome 9.[42]and[43] Identical R849W mutations occurred in the region coding for the tyrosine kinase or TIE-2 receptor.[36]and[47] In addition to this location, later studies have found another Y897S mutation within the TIE-2 gene.[48] Located on the surface of the endothelial cell, TIE-2 is critical to maintaining this multilayer vascular stability between endothelial cells and smooth antagonizes the Ang-1 signal on the TIE-2 receptor, leading to loss of endothelial cell perivascular cell adherence (disassembly), which allows for more sprouting.[35],[49]and[51] In animal models of underexpression of Ang-1, overexpression of Ang-2, or absence of the TIE-2

receptor, vasculogenesis proceeds normally; however, disrupted angiogenesis results in disordered vascular assembly.[49],[50]and[51]

During angiogenesis, freshly sprouted endothelial cells induce the surrounding mesenchyme to express platelet-derived growth factor receptor-β. The new endothelial cells secrete platelet and -derived growth factor B, which interacts with the mesenchymal receptor leading to smooth muscle proliferation and adherence.[54] The interaction between pericyte muscle cells during angiogenesis through activation-inactivation by the angiopoietin (Ang) family of ligands.[44],[52],[49],[53]and[50] Late in angiogenesis (or in nonhypoxic states), Ang-1 produced by the surrounding smooth muscle cell stimulates the TIE-2 receptor on the endothelial cell promoting smooth muscle cell–pericyte proliferation and adherence to the endothelial cells (assembly). Early in angiogenesis (or hypoxemic states) vascular endothelial growth factor leads to the endothelial cell production of Ang-2, which endothelium is also mediated by transforming growth factor-β1 signalling, which is critical for smooth muscle differentiation.

Glomuvenous malformation is an autosomal-dominant inherited subtype of VM resulting in multiple raised purple subcutaneous nodular VMs surrounded by “glomus cells” within the extremities that are painful on palpation.[1],[26],[35]and[46] The entity accounts for 5.1% of all VMs and is inherited in 63.8% of cases.[41] A mutation at chromosome 1p21-22 coding for previously unknown protein glomulin is thought to be responsible.[55] Based on anti–smooth muscle α-actin staining and electron microscopy, glomus cells are thought to be deranged smooth muscle cells.[56],[57]and[58] Glomulin is normally thought to control differentiation of smooth muscle cells by competitively inhibiting inhibitors of the transforming growth

factor-β1 pathway.[46]and[58] In the mutated state, this effect is lost, leading to the glomuvenous malformation phenotype.

Klippel-Trénaunay syndrome has recently revealed three chromosomal abnormalities resulting in “increased” angiogenesis.[61] and [60] Genetic analyses of many other VM-containing syndromes are ongoing.

Clinical Presentation and Diagnosis

The diagnosis of VM and differentiation from other malformations can usually be made purely by clinical history and physical examination. Although all VMs are present at birth,[23] they may not be identified until later in childhood or young adulthood. Usually, the period of greatest enlargement of the lesion occurs from infancy to puberty.[22] Occasionally, the VM may be of insufficient size during the childhood phase of pari passu or commensurate lesional growth and may escape detection. With the end of somatic growth in later adolescence, however, continued linear growth within the malformation often results in clinical manifestations later in life and is typically the case in deeper lesions.[62] Adults presenting with the erroneous label of “acquired” VM on closer questioning often give a history of the formative lesion or related symptoms being present for years to decades earlier.[9] Some have reported accelerated growth because of trauma, hemorrhage, partial resection, or the hormonal influences of pregnancy.[29] and [63]

Those patients with visible VMs are, as expected, the most common referrals to vascular anomaly centers.[8] These lesions are typically soft, compressible variably blue-tinged masses that can enlarge with dependant positioning and Valsalva.[64] The blue tinge is considered pathognomonic and is caused by the known dilated venous channels within the dermis.[22] The lesions

may also possess associated superficial ecchymoses, telangiectasias, or varicosities. Unlike AVMs, there is no hyperemia, increased temperature, pulsatility, or palpable local thrill.

Forty percent of VMs occur in the head and neck region[29]and[63] and may involve mucosal surfaces of the tongue, palate and orbital, mandibular, or neck region. Mandibular lesions typically present as a painless slow-growing masses that infiltrate bony structures, dentition, and affect speech and lead to dysphagia. Local infiltration can cause orbital or ocular issues or airway obstruction.[22]and[65]

Comparative Imaging Diagnosis of Venous Malformations

Although the diagnosis of most cutaneously visible or palpable VMs can be made largely on the basis of clinical history and physical examination, diagnostic imaging is often required for the evaluation of deeper lesions or in the setting of an atypical history to allow differentiation from other malformations or nonmalformation lesions. Imaging may also be performed for confirmation or to alleviate persisting concerns regarding the possibility of malignancy.

Conventional Radiography

Because of limited soft tissue contrast resolution, there is little to be offered by conventional radiography for the evaluation and diagnostic work-up of VMs. Conventional radiography can reveal varying degrees of dystrophic calcification that can commonly occur within VMs and more rarely in LMs.[4] The pathognomonic finding within VMs is the phlebolith caused by thrombosis and calcification.[4],[8], [19], [23], [29],

Ultrasonography

Ultrasound is usually the first modality used in the imaging work-up of a suspected vascular malformation because it is widely available, low cost, noninvasive, and does not use ionizing radiation. On gray-scale imaging, VMs nearly always appear heterogeneous (98%). Relative to adjacent tissue, the lesions are usually hypoechoic (82%), but can be hyperechoic (10%) or isoechoic (8%).[67] Tubular anechoic structures representing vascular channels are seen in a minority of cases (4%–50%).[37]and[67] The pathognomonic phlebolith, as expected, appears as a hyperechoic focus with acoustic shadowing; however, unfortunately this is only detected in 16% of cases.[67] If near the skin surface, the lesions are compressible. On occasion the only sonographic finding is isoechoic skin thickening without discernible mass or vascular channels.[66]

Color and pulsed Doppler analysis of the VMs reveal flow in 84% of lesions, with monophasic and biphasic flow seen in 78% and 6%, respectively. Only 16% reveal no discernible flow, which has been proposed may indicate lesion thrombosis or flow below detectible limits .[67]

Computed Tomography

CT is of limited use in the work-up of most focal VMs because of several factors. CT, even with contrast enhancement, usually provides poor lesion conspicuity relative to adjacent potentially critical structures and does not usually provide assessment of internal malformation vascular architecture, two variables that have significant impact on therapeutic decisions. On noncontrast CT, VMs are usually of low attenuation and appear homogeneous or, as is commonly the case, heterogeneous if infiltrated with adipose tissue.[29] Contrast administration

results in a similar pattern of gradual peripheral to central enhancement as is seen in hepatic

VMs; however, contrast CT can still underestimate lesion extent.[29]and[63] CT scan can identify dystrophic calcifications and phleboliths when present, and can be extremely helpful in providing detailed anatomic information regarding adjacent bony pathology if required.[4]

MR Imaging

The introduction of MR imaging has allowed a giant leap forward in the noninvasive assessment of vascular anomalies by providing superior lesion and soft tissue discrimination to CT, semiquantitative flow assessment, and three-dimensional reconstruction, all without subjecting the patient to ionizing radiation.[4],[68]and[69] As a result, MR imaging has become the imaging modality of choice for these lesions.[68]and[70] Not only can MR imaging influence therapeutic decision making by defining the internal architecture of a malformation and its relationship to adjacent critical structures, but it can also serve an objective method quantitatively to assess therapeutic outcomes through serial MR imaging monitoring of treated lesion size and signal characteristics.[4],[29],[68],[69]and[70] Recent advances now even use MR imaging for image guidance during percutaneous therapy of vascular malformations.[71], [72]and[73] The disadvantages of MR imaging are not unique to malformations, because imaging requires a cooperative, nonclaustrophobic patient and sometimes long scan duration for larger lesions.

The usual basic MR imaging protocol used in the evaluation of a suspected VM should ideally start with a spin-echo or fast spin-echo T1-weighted evaluation of the lesion morphology allowing maximal definition of tissue planes and relationship to critical osseous or neurovascular structures. This should be followed by fat-saturated T2-weighted and T2-weighted short tau inversion recovery sequences, which allow one to define maximal extent of the lesion. T1- and T2-weighted sequences should be performed in at least two planes. The identification of hemosiderin, dystrophic calcification, or phleboliths can be achieved through the use of gradient echo T2 -weighted sequences that can also aid in evaluation of high versus low flow. The study should be completed with pre–gadolinium- and post–gadolinium-enhanced fat-saturated T1-weighted imaging.[4],[29]and[70]

VMs classically appear as either isointense or hypointense[4],[8],[29],[63],[70],[74]and[75] on T1-weighted sequences. They may appear more hyperintense,[76] however, particularly if the lesion contains fat.[75] The lesion can appear focal or diffuse, or demonstrate lobulated margins.[70] A more heterogenous appearance can be identified in the setting of hemorrhage or thrombosis, and often dilated or serpiginous vascular structures can be identified compatible with abnormal veins.[29]and[63] Lower signal areas or signal voids may represent dystrophic calcification or phleboliths on all imaging sequences.[29],[69],[70]and[75] T2-weighed or short tau inversion recovery imaging of VMs consistently demonstrate high signal intensity[4], [8],[29],[63],[70],[74],[75],[76],[77]and[78] and reveal the fullest extent or infiltration at the margins of the lesion, often more so than that defined on T1-weighted imaging. In addition to calcifications or phleboliths, lower signal areas on T2 can be caused by either vascular channels

or fibrofatty septa.[29]and[75] Gradient echo imaging can demonstrate areas of low signal corresponding to calcification or hemosiderin.[29] Gadolinium administration results in homogenous or heterogenous enhancement within the substance of a VM.[70]and[77] Gadolinium-enhanced fat-saturated sequences demonstrate the level of vascularity within the lesion and allow clear separation of the lesion from commonly inspissated or perilesional fat.[4]and[29] MR imaging can be used to monitor clinical outcomes after sclerotherapy with successful treatment resulting in reduction of lesion size.[9]and[37] Treated portions demonstrate increased heterogeneity, decreased T1 and T2 signal intensity, and decreased enhancement, and if necessary, allows for targeting of specific untreated regions for future therapy.[4]an[29]

VMs are usually easily differentiated from other vascular malformations based on several criteria. VMs are differentiated from high-flow malformations because the latter have low T1 and T2 signal and signal void among tangles of hypertrophied arteries, turbulent shunts, and engorged venous spaces that are focally higher signal on gradient echo.[63],[69], [70]and[76] Very importantly, AVMs characteristically lack a definable mass or soft tissue component quite unlike VMs.[70]and[79] Only rarely can an AVM demonstrate a pseudomass because of edema, fatty hypertrophy, diffuse atrophy, or confinement to a fascial compartment.[4] and [80] VMs are readily differentiated from macrocystic LMs because the latter reveal large cystic septated spaces that do not enhance with gadolinium.[63],[70],[76],[77]and[81] Occasionally, the septal walls may enhance causing “rings or arcs” or cyst walls may enhance when inflamed, such as with infection or after sclerotherapy.[70]and[77] Differentiating VMs from microcystic LMs can prove difficult. Because microcystic lesions consist of innumerable small spaces

beyond the resolution of MR imaging, a more homogenous VM-like appearance is seen that may minimally enhance or may not enhance at all.[70]and[77] Because conventional MR imaging is exquisitely sensitive but not specific for the detection and characterization of vascular malformations,[82] all diagnoses have to be made in the context of clinical history and physical examination. As with any other noninvasive imaging, if MR imaging findings are atypical or suspicious or merely nonspecific, one should consider proceeding to diagnostic phlebography or angiography, or biopsy.[4] and [29]

Direct Percutaneous Phlebography

Direct percutaneous phlebography, as the name implies, involves direct fine-needle puncture of the lesion and contrast injection under fluoroscopy and is currently used in several distinct scenarios. The study provides the diagnostic gold standard for specificity in situations requiring confirmation of a VM that may be equivocal on previous imaging modalities, or for treatment planning, or to exclude the possibility of neoplasm in cases where biopsy is being contemplated. The technique can also be used in the evaluation of LMs. More commonly, direct percutaneous phlebography is performed as the initial diagnostic evaluation of venous (or lymphatic) malformation morphology and flow characteristics within the sclerotherapy procedure.[4]and[29]

Diagnostic Angiography

In current practice, there is no role for diagnostic angiography in the diagnostic work-up or management of purely low-flow vascular malformations if one follows a prescribed algorithm.[4]and[83]. Arteriography may have a role in the specialized work-up of mixed lesions that may have a high-flow component.

Historically, arteriography of VMs reveals either no findings, or a delayed mass-associated venous or capillary blush with variable stasis, pooling, or puddling.[4]and[70] Feeding vessels are either normal or slightly enlarged and draining veins may be dilated.[19]

Image-Guided Sclerotherapy of Venous Malformations Rationale

Within a VM, as in any vascular space, the endothelial cell serves as the "center of operations" controlling the local "milieu" of vascular channel growth and function and maintaining and restoring patency through processes of clearance and recanalization.[84] The continued disordered growth controlled at the endothelial cell level is the factor most responsible for VM symptoms bringing patients to medical attention. It stands to reason that, short of resection, only therapy directed at the endothelial cell level is effective.[84]and[85] Because no corrective pharmacologic or genetic endothelial interventions have yet been conceived, only an endothelial-cidal approach can offer the potential to reduce, retard, or eradicate the disease process.

The technique of sclerotherapy induces this local endothelial damage by the selective intraluminal delivery of an endothelial-cidal agent or sclerosant into a chosen abnormal intravascular space that then exerts its injurious effect on the endothelial cell by direct contact in a dose-dependant manner.[8]and[84] Apart from the choice of agent, the therapeutic effect of sclerotherapy on a given endothelial surface is dependant on two major variables: the in vivo sclerosant concentration, and the length of time of sclerosant contact with the endothelial layer or "dwell-time."[4],[83]and[86] In vivo concentration is proportional to in vitro concentration, injection rate, and length of time of agent administration and is inversely

proportional to volume of distribution within the lesion. Lesion flow rate has an inverse proportional relationship with in vivo concentration and dwell time. The flow rate is fortunately low or negligible within VMs, as seen on Doppler[67]; this variable is of only nominal concern. All of these variables can be manipulated to varying degrees to optimize the therapeutic effect on the vascular endothelium of the lesion while minimizing nontarget trauma to nonmalformation structures within and adjacent to the lesion

Major Sclerosing Agents

A number of sclerosing agents have been or are currently being used in the treatment of VMs that vary in degree of relative toxicity, viscosity, and complication profile. A number of sclerosing agents have been or are currently being used in the treatment of VMs that vary in degree of relative toxicity, viscosity, and complication profile

Ethanol is probably the most widely used sclerosant because it is user-friendly, relatively inexpensive, readily available, and has a long shelf-life.[87] and [88] As with all sclerosants, ethanol acts through direct contact with the vascular wall causing dehydration of endothelial cells, precipitation of the cytoplasm, followed by sloughing or denuding of this monolayer. The vascular wall fractures to the level of the internal elastic lamina and blood proteins precipitate.[84] and [89] Given the role of the endothelial cell in angiogenesis and directing removal of thrombus and debris, the elimination of the endothelial cell and its accompanying changes are thought to be responsible, at least by indirect evidence, for the relative permanence of occlusion and lack of recanalization seen after sclerotherapy with ethanol.[84] and [89]

Although ethanol is clearly a highly if not the single most effective agent in achieving vascular closure, it is also very toxic, with a low therapeutic index or ratio, and must be used with extreme caution.[90] The agent must be given with superselective positioning beyond any reasonable doubt as to the possibility of normal tissue between delivery point and target. Nontarget embolization can occur whereby inflow into interstitial tissue leads to rapid penetration of vascular walls and devitalization of normal tissue.[86] and [89] As a result, one of the most common major ethanol-related complications is juxtalesional necrosis, particularly skin necrosis, thought to be the result of reflux into superficial venous channels or capillaries during the sclerotherapy procedure.[91] In addition to skin necrosis, other commonly encountered complications encountered during the treatment of venous or vascular malformations with ethanol include nerve impairment or palsy and hemoglobinuria.[85], [86], [92], [93] and [94] Administration of intravascular ethanol has been noted to cause precapillary pulmonary arterial vasospasm with increased right heart pressures and right heart failure in rare cases.[89] Sustained pulmonary hypertension has been noted in 30% of patients per ethanol treatment session, but does not seem to have a lasting effect, and does not seem to be correlated with total dose administered. There does not seem to be a tendency for increased pulmonary reactivity with multistage ethanol therapy[87] Other rare complications reported are intoxication,[93] bronchospasm,[95] hyperthermia,[96] pulmonary embolus,[85] cardiopulmonary collapse,[97] and death.[98] To reduce the incidence of local and systemic complications, it has been recommended that the administration of ethanol for any given sclerotherapy procedure not exceed 1 mL/kg.[84] In addition to this complication profile, the administration of ethanol is

invariably very painful and usually mandates general anesthesia during the procedure.

Sodium tetradecyl sulphate

Sodium tetradecyl sulphate (STS) is an anionic surfactant that appears as a white waxy solid; however, in injectable form, has a soapy consistency and contains 2% benzyl alcohol.[84] STS is much less toxic than ethanol and acts by causing sludging of erythrocytes; thrombosis of the vessel; and obliteration of the vessel by intimal necrosis, adventitial fibrosis, and luminal collapse.[148] This agent has historically been used extensively in the treatment of esophageal varices and varicose veins; however, after reports of nonvariceal use beginning in the 1980s,[100], [150], [101], [102] and [103] STS has very gradually appeared in the literature for the treatment for VMs.[8], [83], [92], [90] and [99] STS clearly results in lower rates of skin necrosis, nerve impairment, and systemic complications.[83] and [99] In higher doses, however, urticaria, anaphylaxis, and hematuria have been reported.[92] This agent has been found to be less effective at permanent closure of vascular structures within high-flow lesions.[84] Similarly, within VMs, a lower rate of permanent closure is observed,[8] and [90] with larger versus smaller venous cavities demonstrating recurrence.[83]

Polidocanol

Polidocanol is an increasingly popular nonionic surfactant that was initially developed as a topical anesthetic in 1936 but was later found to have a vascular sclerosing effect that made it unsuitable for parenteral use.[104] and [105] Being an anesthetic agent, its intravascular use is virtually painless; however, 1% lidocaine can be added to the agent to ensure minimal pain.[106] Polidocanol consists of 95%

hydroxypolyethoxydodecane and 5% ethanol as a preservative, and is available in concentrations ranging from 0.25% to 4%.[104], [107] and [108] This detergent agent acts by causing rapid overhydration of endothelial cells, with consequent vascular injury and closure, and has direct effects on the intrinsic pathway of coagulation.[109] It does not incite as much endothelial damage as ethanol, STS, or ethanolamine oleate.[110] As such, there has been a relatively low rate of reported local complications, such as skin necrosis or nerve impairment; however, they can occur.[104] and [111] Systemic complications of hemolysis and hemoglobinuria and elevation of D dimers and thrombin-antithrombin III are relatively common[112]; however, more significant events, such as reversible cardiac arrest, have been reported.[113]

Ethanolamine oleate

Ethanolamine oleate is a salt of unsaturated fatty acids and, like other sclerosants, has been used previously in the treatment of gastroesophageal varices and works by two simultaneous mechanisms. The oleic portion of this agent induces a dose-related inflammatory response within the intima and penetrates the vascular wall, leading to a dose-related extra vascular inflammatory reaction and activating coagulation. The ethanolamine portion suppresses fibrin clot organization. In combination, the agent allows fibrosis and sclerosis to replace the lesion that may progress over time and appear in delayed manner.[114], [115] and [116] Ethanolamine oleate may have less of a penetrative effect beyond the vascular wall, particularly where a nerve runs along the lesion in question, and may have a wider safety margin than ethanol.[117] Ethanolamine oleate has been used in both high-flow[117] and [118] and low-flow vascular

malformations[72], [86], [115] and [119] and is thought to have a low incidence of distal embolization.[118] This sclerosant has been known to cause intravascular hemolysis, renal insufficiency, and hepatotoxicity in higher doses, however, and prophylactic haptoglobin administration may be necessary.[69], [86] and [117] To avoid this complication, some have recommended using no more than 1 mL of 5% ethanolamine solution[120] and diluting the solution to 2.5% or 1.25% with the added benefit of less local irritation.[115]

Alcoholic solution of zein

Alcoholic solution of zein is composed of zein solution, sodium amidotrizoate, oleum papaveris, and propylene glycol. The zein solution is made of a water-insoluble prolamine from corn gluten used to form the hard clear shells for coating foods and pharmaceutical products, creating a very viscous solution. Once administered, alcoholic solution of zein requires approximately 10 to 15 minutes to solidify. The agent then remains relatively static in the lesion without passing into venous outflow and is allowed to exert a sustained sclerosant effect leading to necrosis, thrombosis, and fibrosis over the extended dwell time.[121] and [122] Alcoholic solution of zein is then degraded into amino and glutamic acids over approximately 11 days. Alcoholic solution of zein has been used to good effect within VMs.[121], [123], [124] and [125] The material also has been used in LMs and AVMs.[124], [126] and [127] The disadvantages of alcoholic solution of zein include its relative unavailability, usual need for general anesthesia, and possible delayed extrusion of the embolic material to the skin surface.[121] and [126] As such it is no longer considered a first-line agent.

Sodium morrhuate

Sodium morrhuate is sodium salt of fatty acids in cod liver oil that was originally used to treat arthritic joints and varicose veins as a sclerosant, and has been used within VMs.[90] It has been found, however, to be 1.5 to 4 times less effective than STS.[101]

Historically, many other sclerosing or fixative agents have been used either within VMs or for other pathologic cystic phenomena including hypertonic 50% dextrose, hypertonic saline, acetic acid, methylmethacrylate, triamcinolone, bleomycin, and tetracycline.[128]

Direct Percutaneous Phlebography Technique

Direct percutaneous phlebography and sclerotherapy should be performed in an angiography suite equipped with digital angiographic capabilities, real-time ultrasound, and an “in-room” ability to review and correlate with prior MR imaging or angiographic imaging. Except for the rare instance where diagnostic imaging is equivocal for VMs and direct diagnostic phlebography is performed as a purely diagnostic test, the patient usually requires at least conscious sedation and possibly local or regional block or general anesthesia. The patient is then positioned to allow best access to the lesion, and draped and prepared in a sterile fashion leaving all relevant access points to the lesion exposed.

A standard instrument tray is assembled with the addition of clearly labeled syringes or containers of saline, iodinated contrast, and sclerosants. A 20- to 27-gauge needle with short low-volume connector tubing or a butterfly needle is connected to a saline-filled syringe by a three-way stopcock. Whether

for purely diagnostic purposes or as a prelude to sclerotherapy, the direct percutaneous phlebogram classically begins with the percutaneous introduction of the needle into the substance of the VM under real-time ultrasound guidance[29] and [112] with or without fluoroscopic correlation.[130]

For the period of sclerosant administration, removal of the saline syringe and addition of a second three-way stopcock with dual sclerosant syringes facilitates easy syringe exchanges that do not disturb the often precarious needle position within the canalicular channels of the VM).[92] Once the VM has been adequately opacified with iodinated contrast and note is made of both volume of distribution and rate of flow, the chosen sclerosant is gently injected into the lesion at a corresponding rate and volume that gradually displaces the contrast from the region of the VM being treated.[4], [92] and [90] Intermittent aspiration should be performed to ensure a flashback of red blood is present, indicating maintenance of intravascular position and incomplete occlusion of the channel in question.[92] As venospasm and vascular occlusion occur within the regions of the lesion that come into contact with the sclerosant, new pathways or territories may appear. Sclerosant delivery may be continued, or may require additional contrast to define better a new territory before continuing. Careful observation and monitoring is required during sclerosant delivery to assess for extravasation; overly rapid efflux of sclerosant into the venous outflow; resistance to injection; cessation of flashback of red blood; signs of major patient distress; or signs of skin blanching, which may indicate chemical toxicity or ischemia to the skin. Any one of these findings should prompt immediate cessation of further injection of sclerosant.[78], [90] and [129] If palpable, the operator should observe the degree of induration of the lesion over the course of sclerotherapy[99] and [130] and limit

administration as the lesion becomes firm. The vascular territory defined by phlebography on any given needle pass may only represent a portion of the lesion; repeated comparison should be made with the MR image or ultrasound in deciding if multiple needle placements for sclerotherapy are warranted.[83],[90] and [131] The procedure is terminated once an adequate volume of the VM is treated, if maximum allowable sclerosant dose is reached,[90] or if the presence of intravascular or extravascular contrast obscures visibility of the lesion such that safe intraluminal sclerosant delivery cannot be ensured.

The maximum allowable doses for ethanol are 1 mL/kg[84]; however, this dosage is rarely if ever reached. The maximum manufacturer's recommended dose of STS (for varicose veins) is 3 mL of 3% solution; however, some authors recommend a greater maximal allowable dose.[90] Quoted maximal doses for polidocanol (for varicose veins) are 2 mg/kg/d,[113], [132] and [133] or 6 mL of 3% polidocanol solution.[111] Some advocate a maximum of up to 300 mg or 10 mL of 3% polidocanol solution, however, in the treatment of VMs.[107]

Once administration of sclerosant has been completed and the lesion has been treated to the previously described end points, tourniquets or pneumatic cuffs, if used, can be left in place for 2 to 10 minutes to maximize dwell time and sclerosant effect.[90], [106] and [107] The sclerosant needles should be left in situ while the tourniquet or cuff is in position to avoid a significant increase in pressure within the lesion that could lead to extravasation and necrosis.[90] If there is fear of an overly large volume of sclerosant exiting into the general circulation by draining veins on deflation of the tourniquet or cuff, the lesion can be aspirated through the sclerosant needle used to deliver the agent before deflation.[107] If it is

suspected that a quantity of sclerosant has entered into the normal deep venous system, limb elevation and flushing of the system with an intravenous infusion more distally may lessen local injury. After final evaluation of the site by palpation and inspection for signs that may portend skin necrosis, such as blanching, ecchymoses, or retarded capillary refill, the needles can be removed. To allow vascular wall apposition and reduce intralesional volume and dilution effects, compression can be applied to the lesion immediately afterward. Direct compression can be applied merely for several minutes within the procedure room.[101] and [134] Many advocate some form of sustained compression with a dressing for 24 hours[83] and [106] to 3 to 7 days,[90] and [112] however, supplemented with elevation of the involved limb for 24 hours[83] To commence anti-inflammatory therapy, ketorolac, 10 mg, can be administered parentally in the case room. If a significant quantity of ethanol was used as the sclerosant, some have advocated drawing a serum ethanol level.[134] Immediately before the patient leaves the procedure room, a final examination of cutaneous and vascular integrity of the treated region should be performed and documented, including a perfunctory sensory motor function assessment if possible based on the patient's level of consciousness.

If sclerotherapy is contemplated in a superficial malformation, it is recommended that the needle be advanced through normal adjacent tissue en route to the lesion to avoid blood loss or extravasation along the tract during and after sclerotherapy.[92] If the lesion is in close proximity to a nerve, a needle approach as far away as possible from the nerve is recommended and, if sclerotherapy is contemplated, intraprocedural nerve monitoring is recommended.[74] As the needle is slowly advanced toward and into the

malformation, the syringe is gently and continuously aspirated on, until a flashback of blood is observed signifying intraluminal position of the needle.[4], [29] and [90] Once the flashback is observed, the needle tip is stabilized, and very minimal contrast is gently injected to confirm intraluminal and intralesional positioning. Then, low frame-rate digital subtraction phlebography or venography is performed during gentle contrast injection to confirm the presence or absence of VM and to establish that stable intraluminal access has been achieved.[28] and [90].

The optimal spacing between sclerotherapy sessions, should the lesion require, ranges from 3 weeks to 3 months[29], [90] and [134] and may be preceded by an additional ultrasound examination[106] and [111] to evaluate the level of flow and regional involution to direct further therapy. Routine ultrasound evaluation of all patients at 1 month can be performed[106] and provides the opportunity to reassess the patient and assess level of satisfaction and need for further therapy. Although some have advocated MR imaging follow-up as early as 1 to 3 months,[107] significant inflammatory changes within the lesion as a result of sclerotherapy need to resolve and involute before management decisions can be based on its findings. Except in very specific circumstances, MR imaging follow-up should occur 6 full months after the last sclerotherapy session[29] MR imaging evaluation should demonstrate decreased lesion size, decreased T1 and T2 signal intensity, and decreased enhancement in successfully treated regions, and allows for specific targeting of unchanged regions on future sclerotherapy sessions if necessary.[4] and [29] After the MR imaging, a further in-person patient visit can then be scheduled, preferably in a multidisciplinary setting, where lesion tape-

measurements, medical photography, review of imaging, and a discussion of the patient's status and expectations can guide further management if necessary.

Complications of Sclerotherapy

Complications resulting from sclerotherapy of VMs can be classified as minor and major, or local and systemic. Minor local complications include erythema, swelling, pain, and tenderness. Skin blistering can resolve completely or evolve into hyperpigmentation, skin ulceration, and necrosis; however, these complications are still considered to be minor in the literature.[135] and [90] Major local complications can include transient or permanent nerve impairment or paralysis, thrombophlebitis, deep venous thrombosis, muscular contracture,[106] and compartment syndrome. Major systemic complications of sclerotherapy for VMs, both observed and theoretic, include hemolysis, renal toxicity, pulmonary embolism, ocular disturbances, anaphylactic reactions, hypotension, bradyarrhythmia, and cardiopulmonary collapse[29] Because most patients undergo multisession therapy; per patient complication rates are always significantly higher than per session rates.

Choice of sclerosant is the most important variable in the quoted rates of complications. Ethanol is probably the most commonly used sclerosant in the treatment of VMs and, although probably the most efficacious, is clearly associated with the highest rates of complication.[4], [90] and [107] In by far the largest reported series using ethanol in 87 patients over 379 sessions,[135] minor and major complications occurred in 12.4% of sessions and 27.9% of patients. A total of 8.8% of sessions resulted in erythema, blistering, or localized skin or

subcutaneous ulceration or necrosis that resolved with conservative management. A total of 1.5% resulted in deeper injury requiring surgical intervention. Transient and permanent nerve injury occurred as a consequence of 0.8% and 0.5% of sessions, respectively.

Deep venous thrombosis and pulmonary embolism occurred in 1.25% and 0.25% of sessions, respectively. Minor limited chronic musculoskeletal symptoms occurred in 8% of patients, requiring conservative therapy, whereas 1.1% of patients experienced contracture requiring surgical correction. No evidence of transient pulmonary hypertension was identified in the 379 sessions. Other series using exclusively ethanol as the sclerosant for VMs quote complication rates that are consistent with those mentioned previously.[110], [136], [137], [131] and [134]

Significantly lower complication rates are observed with STS sclerotherapy compared with ethanol. In the largest series to date using exclusively tetradecyl sulphate foam in 72 patients over 226 sessions,[90] no major complications were observed. Minor complications occurred in 3.1% of sessions and 9.7% of patients. Complications included ulceration or skin necrosis in 2.2% of sessions or 6.9% of patients and either transient sensory deficit or urticaria, each occurring in 0.44% of sessions and 1.4% of patients. Other than venous thrombosis leading to monocular blindness from treatment of a juxtaocular lesion in a single patient,[148] other studies using tetradecyl sulphate have observed comparably low purely minor complication rates ranging from 0% to 14%.[83], [99] and [101]

Even lower complication rates have been observed with polidocanol sclerotherapy of VMs. Pain and marked swellings are the most commonly

encountered complications, occurring in 82% and 75% of patients, respectively. A total of 22% of treated patients can exhibit local erythema and induration.[106] Transient hyperpigmentation has been observed in 8% with epidermal necrosis or skin blistering occurring in 0% to 0.7%.[106], [107], [111] and [112] Skin necrosis (6%–7% of patients) or inadvertent intra-arterial injection has been observed, resulting in necrosis or nerve impairment (4% of patients).[104] and [111] Transient limb numbness, hypotension, and bradyarrhythmias,[107] and reversible cardiac arrest,[113] have been described during the treatment of VMs with polidocanol. Sclerofoam has been observed traversing a patent foramen ovale (that is present in 20%–25% of adults) and may be responsible for rare transient ocular disturbances described in the varicosity literature. No definite right-to-left shunting complications have yet been described, however, during polidocanol foam treatment of VMs.[104]

Ethanolamine oleate therapy results in mild erythema and inflammation in most patients for up to 72 hours with no significant reports of necrosis or nerve impairment.[72], [86] and [115] Similarly, in the largest series using alcoholic solution of zein for sclerotherapy of VMs,[121] pain, swelling at the injection site, and low-grade fever were the most common complications. A total of 5% of patients experienced skin necrosis and focal extrusion of the alcoholic solution of zein contents, however, and 2.6% developed superficial thrombophlebitis. No significant complications have been reported in smaller series.[123] and [125]

Therapeutic Efficacy of Sclerotherapy

Many clinical and imaging variables enter into the equation of determining degree of therapeutic benefit after sclerotherapy of a VM, making comparison between conservative, surgical, and various interventional radiologic treatment arms difficult. Most studies evaluating efficacy are retrospective and without objective pain scoring systems, which then introduce patient and investigator bias. Clinical outcomes are commonly divided into relatively arbitrary categories, such as excellent, good, fair, poor, or worse, based on reported patient symptoms that may also incorporate imaging based on change in lesion size. Relatively objective prelesion and postlesion size measurements obtained clinically and by imaging, however, are not necessarily well correlated with reduction in malformation-associated symptoms.[90] It is also known that malformation size can be dynamic, and can change with dependent positioning and exercise at times of maximum symptoms and is difficult to assess by static resting state MR imaging. The total number of studies evaluating sclerotherapy of VMs is still relatively small and there are no prospective randomized trials between sclerosants or techniques. There are very few studies that correlate lesion morphology or location with outcome. Because of these issues, it is not surprising that no sclerosant or technique has yet proved itself to be clearly superior.[9]

Despite these shortcomings, certain general trends predicting benefit can be derived based on lesion morphologic characteristics. As previously described by Dubois and coworkers,[29] better results of sclerotherapy have been observed with cavitary lesions and dysmorphic VMs; however, dysmorphic lesions are

more prone to recurrence. Spongy pattern malformations are more difficult to treat, especially if intramuscular. With respect to the MR imaging grading system described by Goyal and coworkers,[78] a lower grade was clearly correlated with better response during ethanol sclerotherapy. Within grade 1 lesions, 71% had excellent response and none had a poor response. Grade 2A lesions demonstrated 22% excellent and 33% poor response. Grade 2B lesions had 27% excellent and 60% poor response. Grade 3 lesions revealed a not surprising 0% excellent response and 57% poor response.

Quality of life assessments have been performed in patients undergoing ethanol sclerotherapy compared with matched controls, and have determined that most patients had decreased symptoms and did well posttherapy.[137] Poorest outcomes were in those patients in whom the VM occupied an entire muscle or compartment.

Predictions of recovery period and therapeutic effect after sclerotherapy for VMs have been reported based on the level of swelling postethanol treatment. In patients in whom there was marked swelling posttreatment, 80% had a prolonged recovery period and 100% had marked therapeutic effect. In those without marked swelling, 6% had prolonged recovery and 76% had therapeutic effect.

In the largest of series using purely ethanol sclerotherapy for VMs,[135] 87 patients receiving on average three sessions of therapy over 8.2 months, with an average follow-up of 18.2 months, and greater than 24 months in 72, technical success was observed in 95% of sessions with no evidence of recurrence. Fair to

good outcomes as defined earlier[136] were observed in 95.4%, and poor in 4.6%. Other studies using ethanol report good to excellent results in 53% to 100%.[110], [137], [129], [131] and [134] In the largest series using purely STS sclerotherapy,[90] 72 patients received an average of 3.1 sessions, with an average follow-up of 41 months. A total of 15% of patients became asymptomatic, 28% had a good response, 24% were improved, 28% were unchanged, and 5.6% worsened. Pretherapy and posttherapy MR imaging performed in approximately half the patients revealed the VM had decreased in size in 54%, was unchanged in 31%, and had increased in size in 14%. Size reduction did not seem to correlate with symptomatic improvement. Other studies using STS alone or in conjunction with other therapies demonstrate patient benefit with moderate or excellent results in 68% to 86%.[83] and [101] Clinically significant therapeutic benefit of polidocanol sclerotherapy, as defined in a number of studies, ranges from 78% to 100%.[154], [106], [107], [111] and [112] Ethanolamine oleate therapy within VMs has produced significant response in 87.5% to 100%.[72], [86] and [115] In the largest series using alcoholic solution of zein,[171] excellent results were present in 74% of patients, with complete cure in 50% of cases. Other smaller alcoholic solution of zein series state complete therapy with sclerotherapy alone in 38% to 100% of patients.[123] and [125]

RESULTS AND ANALYSIS

This was a one and half years prospective clinical study conducted to evaluate the role of direct percutaneous ethanol instillation in the treatment of venous malformations in the face and neck. Total 15 patients were included in the study. The results were analysed under the various headings are given below:

Demographic Profile

Distribution according to age

Seven (46.6%) patients were in the age group of 16 - 25 Years and the mean age was 25.53 ± 13.752. (Table 4)

Table – 4

Distribution of patients according to the age group

Age (years)	n=15	%
5 - 15 years	2	13.3
16 - 25 Years	7	46.6
26 - 35 Years	2	13.3
36 - 45 Years	2	13.3
>45 Years	2	13.3
Mean ± SD	25.53 ± 13.752	

Distribution according to sex

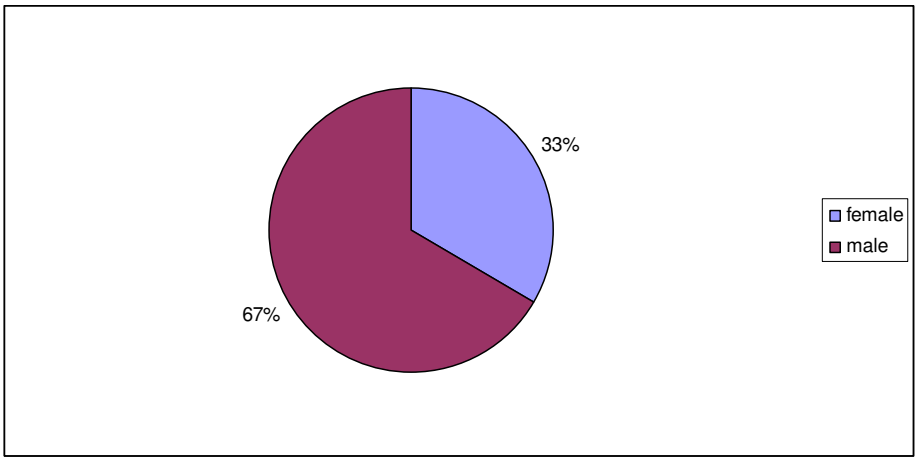
The number of male patients was 10(66.7%) and female patients were 5 (33.3%). The male: female ratio was 2:1. (Table 5 & Fig.5)

Table – 5
Distribution of patients according to sex

	Frequency	Percent
F	5	33.3
M	10	66.7
Total	15	100.0

Fig-5

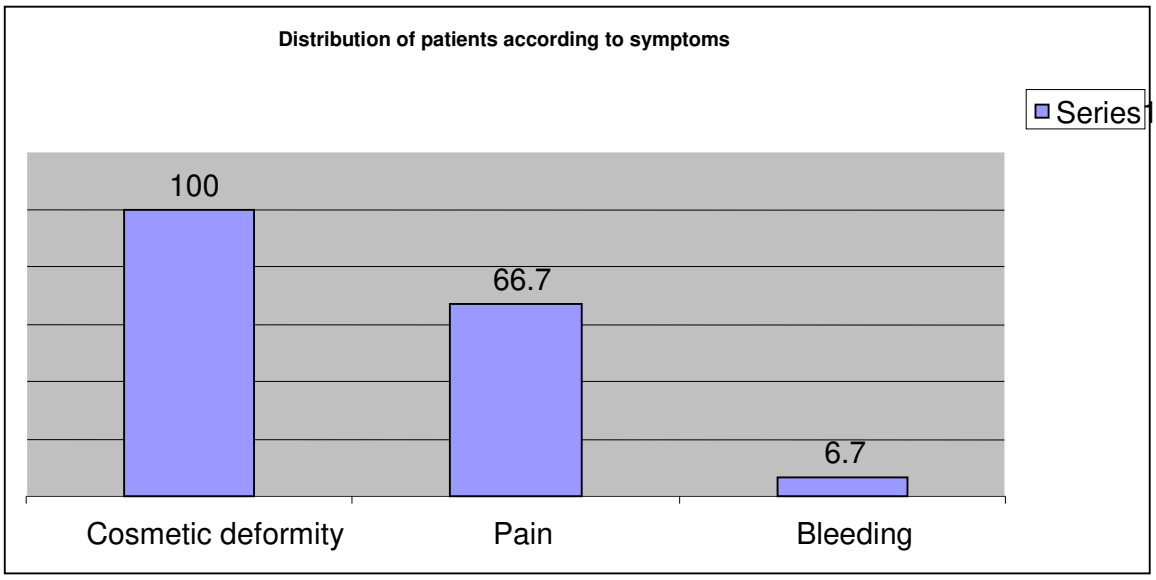
Distribution of patients according to sex



Distribution according to symptoms

All the 15 (100%) patients presented with cosmetic deformity while 10(66.7%) patients presented with pain and one (6.7%) with bleeding. (Fig.6)

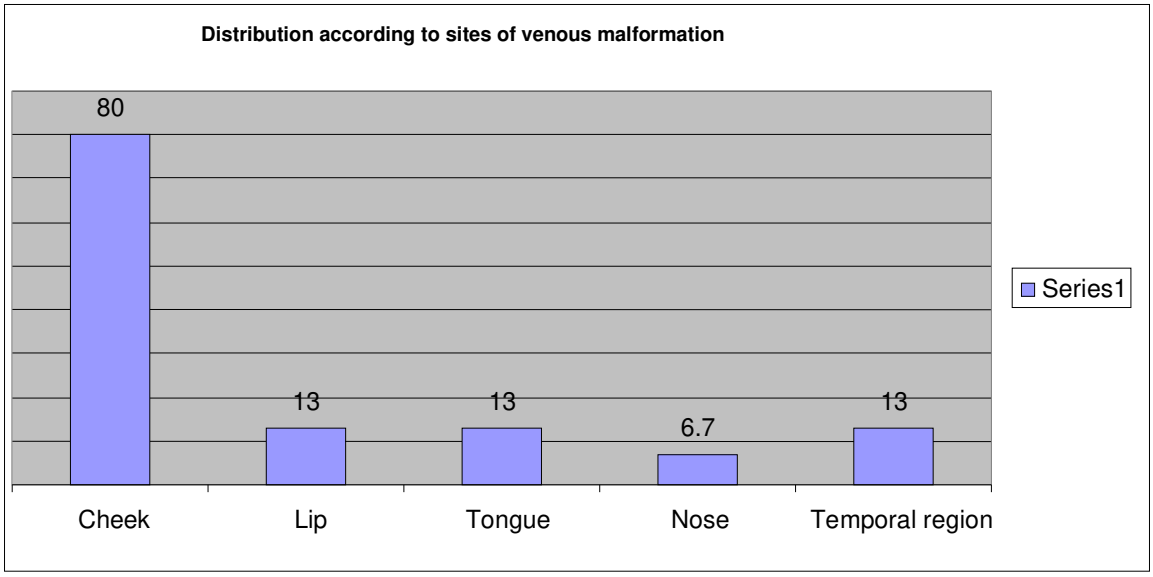
Fig – 6



Distribution according to sites of venous malformation

The lesion was present on the cheek in 12(80%) of patients while only one (6.7%) patient presented with nose lesion. (Fig.7)

Fig - 7



Distribution according to number of sclerotherapy sessions

Eleven (73.3%) patients needed only one session of sclerotherapy while 2(13.3%) each, required 2 and 3 sessions respectively. (Table 6)

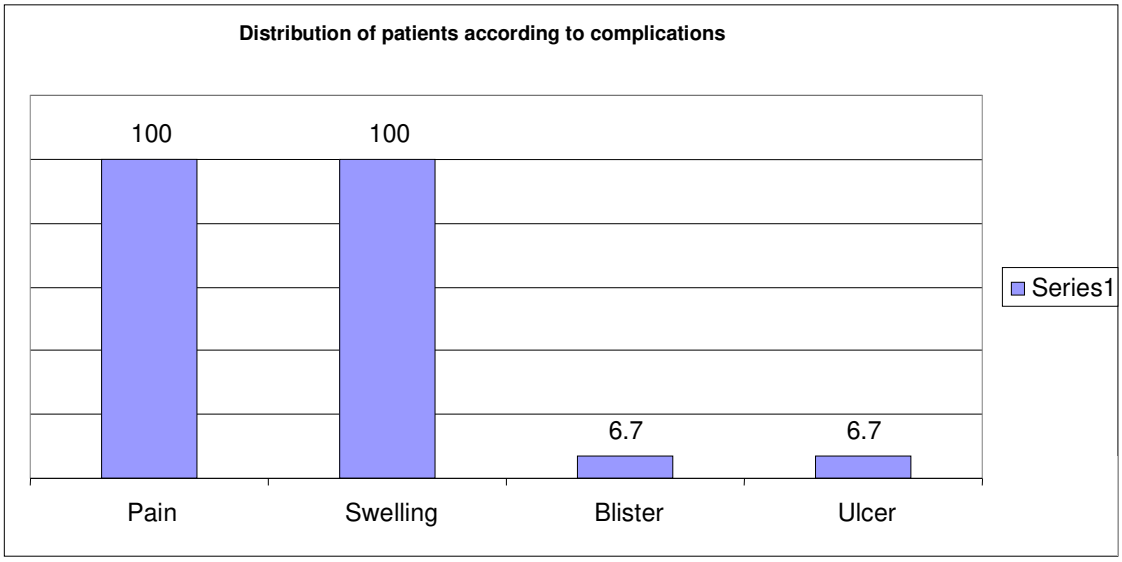
Table – 6
Distribution according to number of sclerotherapy sessions

No. of sclerotherapy sessions	n = 15	%
1	11	73.3
2	2	13.3
3	2	13.3
Total	15	100.0

Distribution according to complications

All the 15 (100%) patients developed post injection swelling and pain while one (6.7%) patient each developed blister and ulcer respectively. (Fig.8)

Fig – 8



Distribution according to follow up

The maximum follow up was 14 months and minimum was 3 months with mean of 7.6.

Comparison of pre and post injection volume

The maximum pre injection volume was 48ml and minimum was 4.5ml with median 21.the maximum post injection volume was 21 and minimum was 1ml with median 6. (Table 7)

Table – 7

Comparison of pre and post injection volume

Pre inj vol(ml)	Post inj vol(ml)
35	8
48	8
10	3
12	4.5
38	8
36	9
14	5
10	3
6	2
22	7
27	7
21	6
32	21
21	6
4.5	1

T-Test for pre and post injection volume

Pre -Post Analysis

Comparing the median values 21 and 6; p value was found to be .000 which is highly significant. That is, there is a significant difference between the volumes (pre inj and post inj)

(Table 8, 9 and Fig.9)

Table - 8

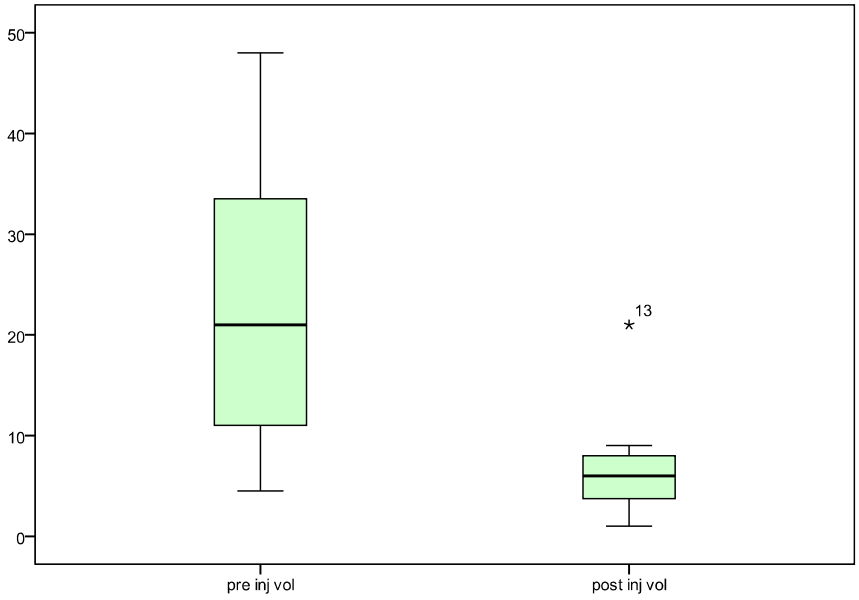
		Mean	N	Std. Deviation	Std. Error Mean
Pair 1	pre_inj_volume	22.43	15	13.189	3.405
	post_inj_vol	6.57	15	4.671	1.206

Table – 9

		Paired Differences					t	df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference				
					Lower	Upper			
Pair 1	pre_inj_volume - post_inj_vol	15.867	10.827	2.796	9.871	21.863	5.676	14	.000

Fig – 9

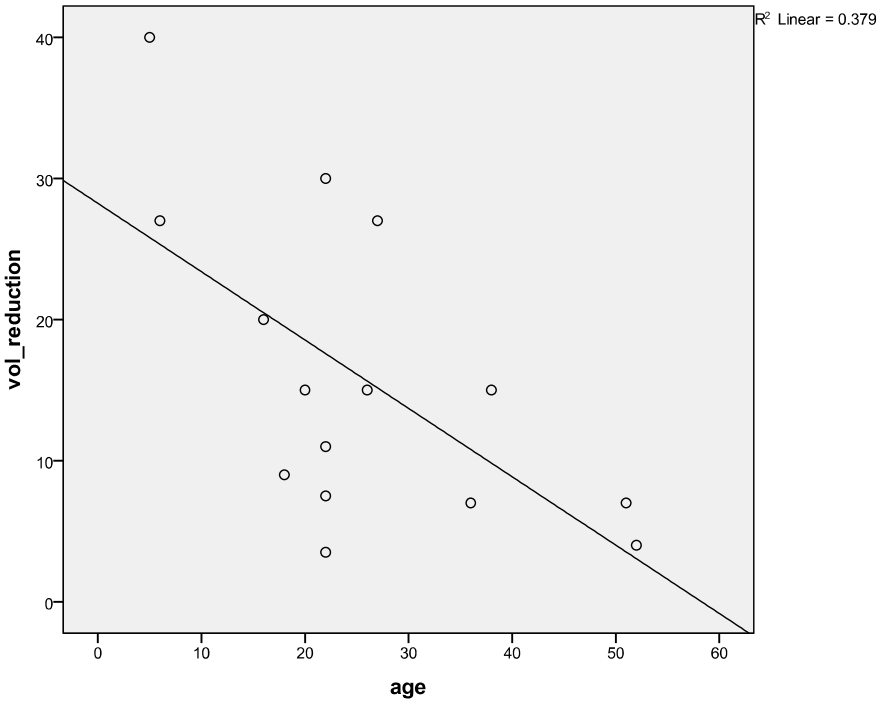
Box Plot – Pre and post of injection volumes



Correlation of Age with Volume Reduction

The scatter plot shows as age increases vol reduction is less for which Spearman's rank correlation coefficient, r= -0.543 which is significant.

Fig - 10



Grading of Lesions

In our study, 4(26%) patients showed good results while 9(60%) had fair results. (Table 10)

Table – 10
Grading of Lesions

Good	4(26%)
Fair	9(60%)
Poor	1(6.7%)

Discussion

A vascular malformation is composed of dysmorphic vessels that are believed to be the result of faulty embryonic development. Depending on predominant channel they are subcategorized as arterial, capillary, lymphatic, and venous or combined[92] .Out of all these subcategories venous malformations are found to be most common.

Venous malformations are common particularly in head and neck region. They present a wide spectrum, from isolated cutaneous or intramuscular varicosities to more complex anomalies involving several tissue planes. The most common site found in our series was cheek which is similar to study by Berenguer B et al[138]. With lesions in the face and neck, patient concern focuses on cosmetic considerations more than functional difficulties.[139] Symptoms vary depending on the location of the lesions, which are soft, compressible, nonpulsatile masses that may cause sudden pain, and which may exhibit development of a firm mass that subsides within days.[92] and [138] Even small venous malformations can cause severe pain. The most common presentations in our study were cosmetic deformity and pain which was similar to study by Berenguer B et al[138] and Lee CH et al[134].

The diagnosis of venous malformations is based on careful history and clinical examination. MRI can be used to define the extent of the malformations of the face and neck, and define the pathway of venous drainage. [92], [139], [112] and [72] Venous malformations show high signal intensity on enhanced MR images, [112] and [72]which can be used to define the muscles or organs involved.

Venous malformations have been treated by a variety of techniques over the years, including irradiation, electrocoagulation, cryotherapy, intravascular magnesium or

copper needles, surgical excision, lasers, compression, and sclerotherapy. [72, 140 and 141] All these techniques have their particular indications and limitations. Surgical excision is useful only for localised and limited lesions. Aggressive excision can lead to significant loss of motor function, cosmetic problems, nerve damage, or massive bleeding in patients with extensive involvement because of the complicated anatomy of the face and neck. [112 and 136]

Sclerotherapy has the advantage of no external scaring, and few complications in comparison with surgical treatment. There are various choices of agents for sclerotherapy: 5% sodium morrhuate, sodium tetradecyl sulphate, ethanolamine oleate, OK432, bleomycin, ethanol, and hypertonic saline, alone or in various combinations, have all been used.[92, 138, 137] Ethanol is the most of often used due to its low cost, antiseptic quality, wide availability and easy of use; however, ethanol sclerotherapy requires general anaesthesia because the procedure is very painful.[142] Direct percutaneous contrast injection into the cavity is also required to detect the lesion volume and the possibility of multiple compartments.

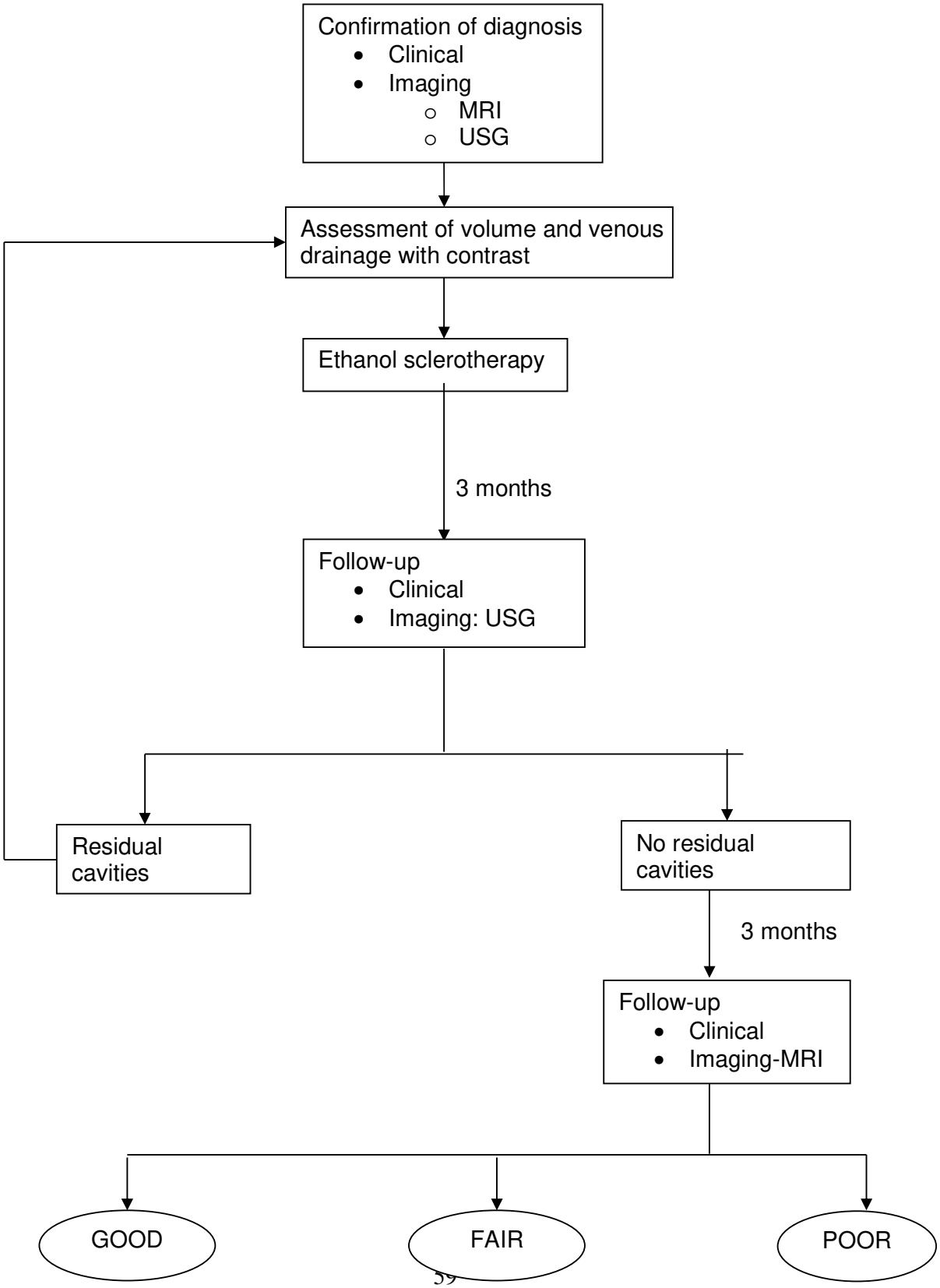
The volume of ethanol to be injected is determined from the percutaneous contrast study. In our patients, one-third of the cavity volume of 99% ethyl alcohol was injected into the tumour cavities. [92, 139 and 134] To achieve the required result and to minimise the flow of ethanol into normal venous drainage structures, we used rubber bands to compress the patients' foreheads and chins to occlude facial venous return. Repeated aggressive treatment is required for very large malformations because recanalisation can occur, and to reduce the risk of major morbidity from the ethanol injection. [92 and 136] In our study, 11(73.3%) patients required only one injection of sclerotherapy while 2(13.3%) each, required 2 and 3 sessions respectively. All patients experienced symptomatic or cosmetic improvement. We attempted to study the factors that might predict the results of sclerotherapy. Only age and volume reduction were valuable

predictors. There was lack of correlation of other variables such as sex, location and number of sclerotherapeutic sessions. Perhaps our failure to statistically confirm these impressions can be ascribed to the small size of our sample. Young patients showed a better response to treatment in our study .The interval between injections is usually 12 weeks, to allow time to determine whether abnormal venous channels persist and to allow local reactions to subside.

Potential complications of sclerotherapy include local skin necrosis, transient nerve palsy, haemoglobinuria, blood loss, and anaphylaxis. [92], [139], [138], [72], [141], [136], [142] and [135] Two patients in this study experienced transient facial nerve palsy, which resolved spontaneously within 3–5 days. The major disadvantage of this treatment is severe complication can rarely occur and include acute pulmonary hypertension with cardio-pulmonary collapse.[142] To avoid such a catastrophic situation, it is suggested to inject the ethanol slowly combined with rubber band compression.[137] and [142] Injection of ethanol produces marked tissue swelling because of a combination of intralesional thrombosis and edema. In our study, there were no major complications. However, all the patients had post injection swelling and pain which subsided over a period of few weeks.

Thus, ethanol sclerotherapy is an effective alternative treatment for venous malformations of the head and neck, and it is wise to begin this treatment as early as possible once the diagnosis is made. Careful planning is essential to reduce the potential risks of the procedure, and long-term follow-up of patients is needed to detect any recurrence.

Algorithm showing the study plan



Fate of Fair and Poor Response category group

All the patients under these categories will be followed up over the next two years. Their lesions will be reassessed every 6 months both clinically and by imaging (ultrasound) for any residual lesion. Any residual cavitatory lesion will be given sclerosant injection while any solid localised lesion will be assessed for surgical excision.

Summary

This was a one and half years prospective clinical study conducted to evaluate the role of direct percutaneous ethanol instillation in the treatment of venous malformations in the face and neck. Total 15 patients were included in the study.

- The Mean age of patients in our study is 25.53 years with age range of 5 – 52 years.
- The male: female ratio in our study was 2:1.
- The most common symptom in our study was cosmetic deformity (100%).
- The most common site was cheek seen in 12(80%) patients.
- 73.3% of patients required only one injection of sclerotherapy.
- There were no major complications in our study.
- The mean follow up was 7.6 months.
- Majority of patients showed significant reduction of volume of the lesion after sclerotherapy.
- Young patients showed better response to treatment.
- According to grading scale, 4(26%) patients showed excellent results while 9(60%) had good results.

Conclusion

Ethanol Sclerotherapy for Venous Malformations of face & Neck is a safe & effective treatment option and the risk of morbidity involved with surgical treatment can be substantially reduced by acceptance of ethanol sclerotherapy by direct percutaneous technique.

Patient Photographs

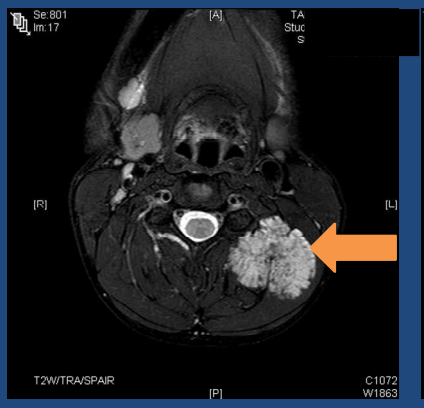
Case - 5

22y M
Venous Malformation Left Neck

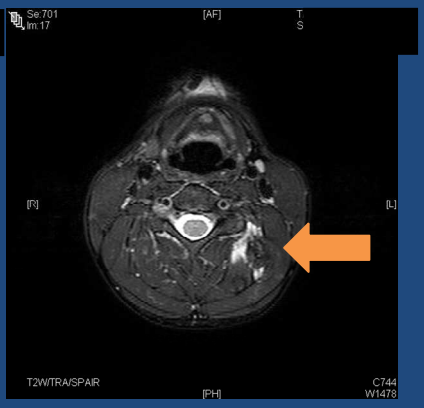
PRE THERAPY

POST THERAPY

Pre Axial

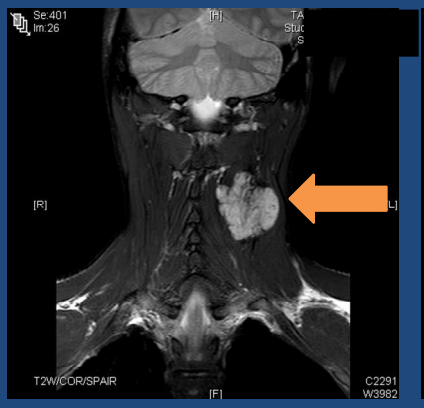


Post Axial

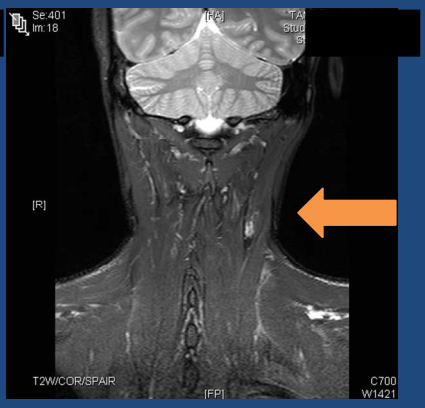


(Contd)

Before Coronal



After Coronal



Case - 6

27y M
Venous Malformation Right Cheek

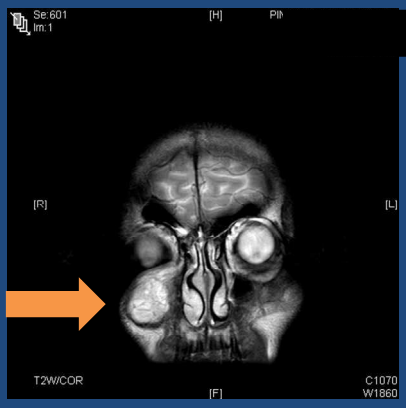
PRE THERAPY

POST THERAPY

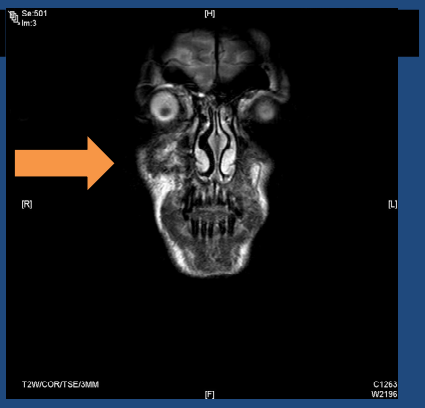
Pre

Post

Pre Coronal

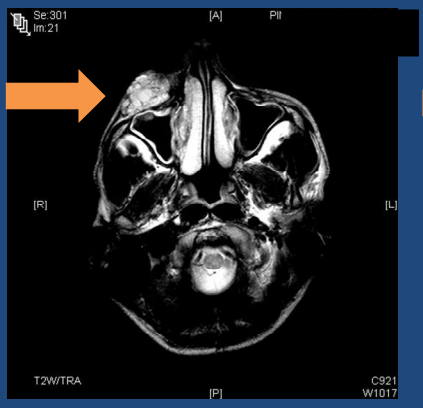


Post Coronal

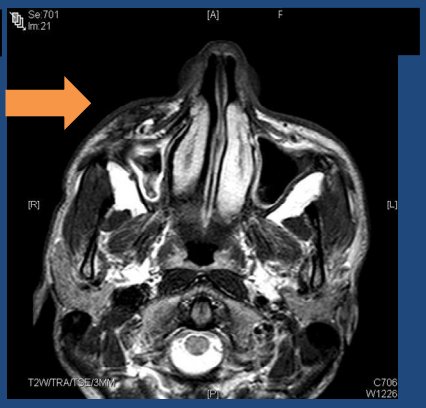


(contd)

Before Axial



After Axial

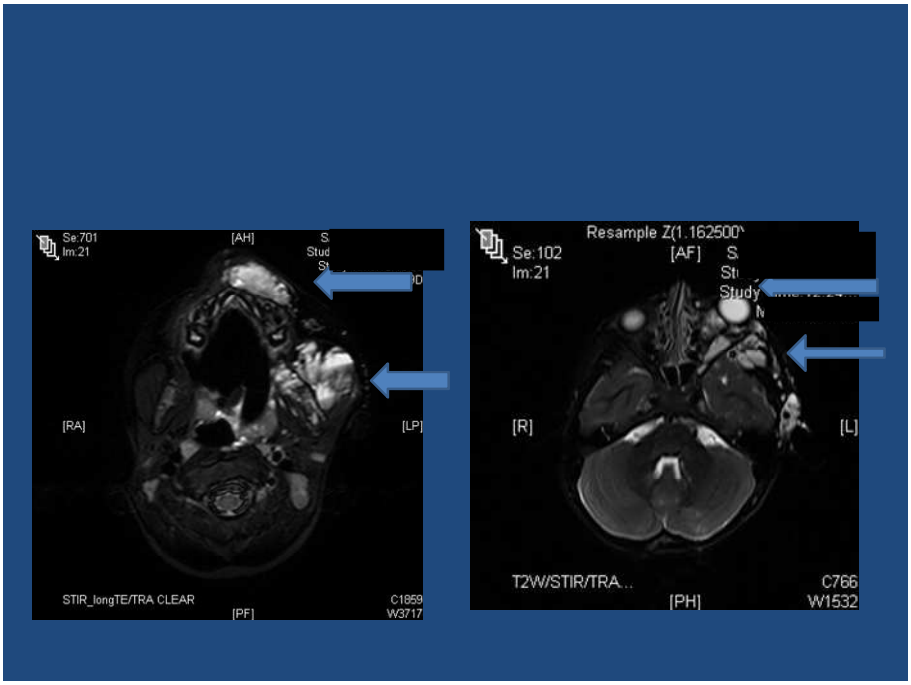


Case - 2

5Y F
Venous Malformation Left Cheek & upper lip

Pre

Post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Im:21
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STIR_longTE/TRA CLEAR
[PF]
C1859
W3717
Resample Z(1.162500
Se:102
Im:21
[AF]
Study
[R]
[L]
T2W/STIR/TRA...
[PH]
C766
W1532

Case - 10

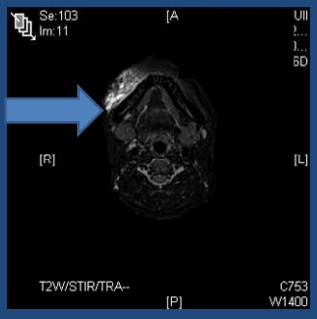

5Y f
Venous Malformation right Cheek
preop
Post op

contd

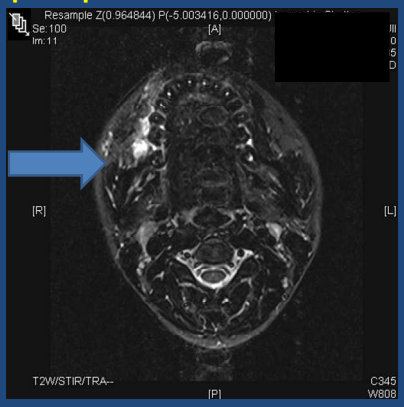
preop

postop

preop



postop



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Christian Medical College, Vellore

Department of Plastic Surgery

A Prospective Non Randomized Clinical Study to Evaluate the Role of Direct Percutaneous Ethanol Instillation in the Treatment of Venous Malformations in the Face and Neck

Information sheet

You are being requested to participate in a study to see the effect of ethanol instillation in the treatment Venous Malformations in the Face and Neck. There are other sclerosing agents that can help with these but ethanol is the most reliable among them with least chances of recurrence. We hope to include about 15 people from this hospital in this study.

How will the treatment with ethanol instillation help you?

Direct Percutaneous Instillation of ethanol will help in obliteration of the malformation to complete or near complete levels thus helping in providing you with relief from your symptoms with the advantage of no external scarring and few complications as compared to surgical treatment**.**

Does treatment with ethanol have any side effects?

Potential risks to participants include local skin discoloration with blistering, transient nerve palsy, blood in urine, blood loss, and anaphylaxis. Rarely it may affect the heart with a potential for cerebral intoxication which can be prevented.

If you take part what will you have to do?

Percutaneous Ethanol (99.5% ethyl alcohol) Sclerotherapy will be used under fluoroscopy guidance using intravenous general anesthesia. You will be examined with Magnetic Resonance Imaging to evaluate the possible remaining extent of venous malformation after 12 weeks. Repeated course of injection 99.5% ethanol may be administered after an interval of 12 weeks from the previous injection if abnormal venous channels persist. Treatment success will be determined by reduction in lesion size.

You will be expected to come for a review to the hospital 12 weeks after first cycle and again after 12 weeks if need be.

Can you withdraw from this study after it starts?

Your participation in this study is entirely voluntary and you are also free to decide to withdraw permission to participate in this study. In addition, if you experience any serious side effects , the study will be stopped and you may be given additional treatment.

What will happen if you develop any study related injury?

We do not expect any injury to happen to you but if you do develop any side effects or problems due to the study, these will be treated at no cost to you. We are unable to provide any monetary compensation, however.

Will your personal details be kept confidential?

The results of this study will be published in a medical journal but you will not be identified by name in any publication or presentation of results. However, your medical notes and photographs may be reviewed by people associated with the study, without your additional permission, should you decide to participate in this study.

If you have any further questions, please ask Dr.Shashank Lamba, Department of Plastic Surgery, CMC, and Vellore. Ph.04164212017. email id : shashanklamba@gmail.com

CONSENT TO TAKE PART IN A CLINICAL TRIAL

Study Title: A Prospective Non Randomized Clinical Study to Evaluate the Role of Direct Percutaneous Ethanol Instillation in the Treatment of Venous Malformations in the Face and Neck

Study Number:

Participant's name:

Date of Birth / Age (in years):

I_____

_____, son/daughter of _____

(Please tick boxes)

Declare that I have read the information sheet provide to me regarding this study and have clarified any doubts that I had. [ ]

I also understand that my participation in this study is entirely voluntary and that I am free to withdraw permission to continue to participate at any time without affecting my usual treatment or my legal rights [ ]

I understand that I will receive free treatment for any study related injury or adverse event but I will not receive and other financial compensation [ ]

I understand that the study staff and institutional ethics committee members will not need my permission to look at my health records even if I withdraw from the trial. I agree to this access [ ]

I understand that my identity will not be revealed in any information released to third parties or published [ ]

I voluntarily agree to take part in this study [ ]

Name:

Signature of the Patient/Parent/Guardian:

Date:

Name of witness:

Relation to participant:

Date:

					Symptoms			site	
sno	age	sex	diagnosis	no of sessions of sclerotherapy	cosmetic deformity	pain	bleeding	cheek	Lip
1	6	f	Venous Malformation Left Cheek	3	y	y	n	y	n
2	5	f	Venous Malformation left Cheek upper lip& temporal region	3	Y	y	y	y	y
3	36	m	Venous malformation left cheek	2	Y	n	n	y	n
4	22	m	Venous malformation Right Cheek lip & tongue	1	Y	y	n	y	y
5	22	m	Venous malformation left neck	1	Y	n	n	n	n
6	27	m	Venous malformation Right cheek	1	Y	y	n	y	n
7	18	m	Venous malformation right Cheek	2	Y	n	n	y	n
8	51	f	Venous malformation Right Cheek	1	Y	y	n	y	n
9	52	F	Venous malformation (R) temporal region	1	Y	y	n	n	n
10	20	F	Venous malformation (R) cheek	1	Y	n	n	y	n
11	16	M	Venous Malformation Right Cheek & tongue	1	Y	y	n	y	n
12	26	M	Venous Malformation Right Cheek	1	Y	n	n	y	n
13	22	m	Venous Malformation Left Cheek	1	Y	y	n	y	n
14	38	m	Venous Malformation Left Cheek	1	Y	y	n	y	n
15	22	m	Venous malformation root of nose	1	y	y	n	n	n

	site		Complication Pain							
site tongue	root of nose	temporal region	Pain	swelling	blister	ulcer	pre inj volume	post inj vol	follow up (months)	
n	n	n	y	y	n	n	35	8	9	
n	n	y	y	y	y	y	**48**	8	9	
n	n	n	y	y	n	n	10	3	12	
y	n	n	y	y	n	n	12	4.5	10	
n	n	n	y	y	n	n	38	8	14	
n	n	n	y	y	n	n	36	9	10	
n	n	n	y	y	n	n	14	5	9	
n	n	n	y	y	n	n	10	3	9	
n	n	y	y	y	n	n	6	2	8	
n	n	n	y	y	n	n	22	7	4	
y	n	n	y	y	n	n	27	7	4	
n	n	n	y	y	n	n	21	6	3	
n	n	n	y	y	n	n	32	21	3	
n	n	n	y	y	n	n	21	6	3	
n	y	n	y	y	n	n	4.5	1	8	